

What is claimed is:

1. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising administration of a controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, for evening dosing every 24 hours containing from about 180 mg to about 420 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a C_{max} of Diltiazem in the blood at between about 10 hours and about 17 hours (T_{max}) after administration of the preparation, the preparation being in a sustained-release dosage form in which the form of Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the form of Diltiazem
- 15 (i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:
 - 20 (a) between about 1% and about 15% after 2 hours;
 - (b) between about 7% and about 35% after 4 hours;
 - (c) between about 30% and about 58% after 8 hours;
 - (d) between about 55% and about 80% after 14 hours; and
 - (e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

- (a) between about 1% and about 25% after about 2 hours;
- 5 (b) between about 7% and about 45% after about 4 hours;
- (c) between about 30% and about 68% after about 8 hours;
- (d) in excess of about 75% after about 24 hours.

2. A method of treating or preventing myocardial ischemia and angina in
10 a patient in need thereof comprising administration of a controlled-release
Galenical preparation of pharmaceutically acceptable form of Diltiazem
including the pharmaceutically acceptable salts thereof, for evening dosing
every 24 hours containing from about 180 mg to about 420 mg of the form of
Diltiazem with excipients to provide controlled (sustained) release of the
15 form of Diltiazem from the preparation for providing a C_{max} of Diltiazem in
the blood at between about 10 hours and about 17 hours (T_{max}) after
administration, the preparation being in a sustained-release dosage form in
which the form of Diltiazem is adapted to be control released after
administration of the preparation over a period of time and being adapted to
15 release the form of Diltiazem

(i) into an aqueous medium at the following rates measured using the
method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of
water:

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- (a) between about 4% and about 8% after 2 hours;

- (b) between about 16% and about 21% after 4 hours;
- (c) between about 44% and about 52% after 8 hours;
- (d) between about 69% and about 76% after 14 hours; and
- (e) and in excess of about 85% after 24 hours;

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and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

- (a) between about 4% and about 15% after 2 hours;
- (b) 10 between about 16% and about 30% after 4 hours;
- (c) between about 44% and about 62% after 8 hours;
- (d) in excess of about 80% after 24 hours.

3. The method of claim 1 wherein the C_{max} of Diltiazem in the blood is
15 obtained between about 11 - about 13 hours after administration of the preparation.

4. The method of claim 2 wherein the C_{max} of Diltiazem in the blood is
obtained between about 11 - about 13 hours after administration of the
20 preparation.

5. The method of claim 1 wherein the preparation is a diffusion controlled preparation.

6. The method of claim 1 wherein the preparation releases the form of Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution.

5 7. The method of claim 1, wherein the preparation is in capsule form.

8. The method of claim 1, wherein the preparation is in tablet form.

10 9. The method of claim 1, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.

15 10. The method of claim 1, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically

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acceptable salt thereof associated with a wetting agent and wherein the form of Diltiazem is mixed with the wetting agent.

11. The method of claim 1 . . . wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the form of Diltiazem is mixed with the wetting agent wherein the wetting agent assists to maintain the solubility of the form of Diltiazem in each bead, ensuring that the solubility of the form of Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.
12. The method of claim 1 . . . wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the membrane comprises a water-dispersible or water-soluble polymer and a

water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

5 13. The method of claim 1 . . . wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent wherein the
10 preparation comprises a mixture of the form of Diltiazem and/or pharmaceutically acceptable salt with the wetting agent and the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which
15 hydrates the preparation.

14. The method of claim 1 . . . wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and
20 the central core comprises the form of Diltiazem or pharmaceutically

acceptable salt thereof associated with a wetting agent wherein the membrane comprises a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester and hydroxypropylmethylcellulose.

5 15. The method of claim 1 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, and wherein the
10 membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the form of diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).

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16. The method of claim 9 wherein the form of Diltiazem is mixed with the wetting agent and the membrane comprises N,N,N-trimethyl-2-[(2-methyl-1-oxo-2-propenyl)oxy]-chloride ethanaminium polymer with ethyl-2-propenoate and methyl-2-methyl-2-propenoate, an acrylic polymer and
20 plasticizer combined to form the membrane thereby providing a mechanism

of release from this membrane which "washes" the form of diltiazem through pores created when the plasticizer incorporated in the membrane, is released in gastrointestinal fluid.

5 17. The method of claim 1 wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises the form of Diltiazem or a pharmaceutically acceptable salt thereof associated with a dissolution agent (other than a wetting agent) to assist in
10 the release of the form of Diltiazem from the preparation.

18. The method of claim 1 wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or a pharmaceutically acceptable salt thereof associated with a dissolution agent (other than a wetting agent) to assist in the release of the form of Diltiazem from the preparation and wherein the dissolution agent is an organic acid selected from the group consisting of adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid, tartaric acid which
15 permits the form of diltiazem to dissolve in gastrointestinal fluids when the microgranules pass into the higher pH regions of the gastrointestinal tract of
20 the intestine at which pH diltiazem is much less soluble.

19. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of said preparation of claim 1 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

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20. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 2 to the patient in the evening for effective treatment or prevention of the myocardial ischemia and angina the next morning.

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21. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 3 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

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22. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 4 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

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23. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 5 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

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24. A method of treating myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 6 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

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25. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 7 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

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26. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 8 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

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27. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 9 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

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28. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 10 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

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29. A method of treating or preventing myocardial ischemia in a patient in need thereof comprising the administration of the preparation of claim 11 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

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30. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 12 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

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31. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 13 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

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32. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 14 to the patient in the evening for the effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

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33. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 15 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

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34. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 16 to the patient in the evening for effective treatment or prevention of the myocardial ischemia and angina the next morning.

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35. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 17 to the patient in the evening for effective treatment or prevention of the myocardial ischemia and angina the next morning.

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36. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 18 to the patient in the evening for effective treatment or prevention of the myocardial ischemia and angina the next morning.

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37. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of said preparation of claim 1 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour period.

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38. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 2 to the patient in the evening for effective treatment or prevention of the myocardial ischemia and angina over a twenty-four hour period.

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39. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 3 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour period.

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40. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 4 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour period.

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41. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 5 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour period.

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42. A method of treating myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 6 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour period.

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43. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 7 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour period.

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44. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 8 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour period.

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45. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 9 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour period.

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46. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 10 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour period.

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47. A method of treating or preventing myocardial ischemia in a patient in need thereof comprising the administration of the preparation of claim 11 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour period.

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48. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 12 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour period.

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49. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 13 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour period.

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50. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 14 to the patient in the evening for the effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour
10 period.

51. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 15 to the patient in the evening for effective treatment or prevention of
15 the patient's myocardial ischemia and angina over a twenty-four hour period.

52. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 16 to the patient in the evening for effective treatment or prevention of
20 the myocardial ischemia and angina over a twenty-four hour period.

53. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 17 to the patient in the evening for effective treatment or prevention of
25 the myocardial ischemia and angina over a twenty-four hour period.

54. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 18 to the patient in the evening for effective treatment or prevention of the myocardial ischemia and angina over a twenty-four hour period.

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55. The method of claim 1 wherein the preparation contains 180 mg of Diltiazem.

10 56. The method of claim 1 wherein the preparation contains 360 mg of Diltiazem.

57. The method of claim 1 wherein the preparation contains 420 mg of Diltiazem.

15 58. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising administration of a controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, for evening dosing every 24 hours containing from about 180 mg to about 420 mg of the form of
20 Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a C_{max} of Diltiazem in the blood at between about 10 hours and about 17 hours (T_{max}) after administration of the preparation, the preparation being in a sustained-release dosage form in which the form of Diltiazem is adapted to be control
25 released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

5 (a) between about 1% and about 15% after 2 hours;
 (b) between about 7% and about 35% after 4 hours;
 (c) between about 30% and about 58% after 8 hours;
 (d) between about 55% and about 80% after 14 hours; and
 (e) and in excess of about 75% after 24 hours.

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and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

15 (a) between about 1% and about 25% after about 2 hours;
 (b) between about 7% and about 45% after about 4 hours;
 (c) between about 30% and about 68% after about 8 hours;
 (d) in excess of about 75% after about 24 hours wherein the preparation comprises a plurality of microgranules, wherein each microgranule comprises a central core of the form of diltiazem or a
20 pharmaceutically acceptable salt thereof, associated with a wetting agent, wherein the central core is coated with a microporous membrane and wherein the wetting agent is selected from the group consisting of:

sugars;

25 saccharose, mannitol, sorbitol;
 lecithins;

C₁₂ to C₂₀ fatty acid esters of saccharose,;
xylose esters or xylites;
polyoxyethylenic glycerrides;
esters of fatty acids and polyoxyethylene;
5 sorbitan fatty acid esters;
polyglycides-glycerides and polyglycides-alcohols esters and
Metal salts.

59. The method of claim 9 wherein the wetting agent is in association with
10 the diltiazem in the microgranule and not mixed therewith, the membrane
comprises a water-soluble or water dispersible polymer or copolymer and a
water-, acid- and base-insoluble polymer which is a neutral copolymer of
acrylic acid ethyl ester and acrylic acid methyl ester enabling the bead to be
hydrated by the introduction of intestinal fluids into the core hydrating the
15 core and therefore mixing the diltiazem and the wetting agent.

60. A method of treating or preventing myocardial ischemia and angina in
a patient in need thereof comprising the administration of the preparation of
claim 58 to the patient in the evening for effective treatment or prevention of
20 the patient's myocardial ischemia and angina the next morning.

61. A method of treating or preventing myocardial ischemia and angina in
a patient in need thereof comprising the administration of the preparation of
claim 3 to the patient in the evening for effective treatment or prevention of
25 the patient's myocardial ischemia and angina the next morning wherein each
microgranule comprises a central core of the form of diltiazem or a

pharmaceutically acceptable salt thereof, associated with a wetting agent, wherein the central core is coated with a microporous membrane and wherein the wetting agent is in association with the diltiazem in the microgranule and not mixed therewith, the membrane comprises a water-soluble or water dispersible polymer or copolymer and a water-, acid- and base-insoluble polymer which is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester enabling the bead to be hydrated by the introduction of intestinal fluids into the core hydrating the core and therefore mixing the diltiazem and the wetting agent.

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62. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 3 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour period
15 wherein each microgranule comprises a central core of the form of diltiazem or a pharmaceutically acceptable salt thereof, associated with a wetting agent, wherein the central core is coated with a microporous membrane and wherein the wetting agent is in association with the diltiazem in the microgranule and not mixed therewith, the membrane comprises a water-soluble or water dispersible polymer or copolymer and a water-, acid- and base-insoluble polymer which is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester enabling the bead to be hydrated by the introduction of intestinal fluids into the core hydrating the core and therefore mixing the diltiazem and the wetting agent.

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63. A method of treating or preventing myocardial ischemia and angina in
a patient in need thereof comprising administration of a controlled-release
Galenical preparation of pharmaceutically acceptable form of Diltiazem
including the pharmaceutically acceptable salts thereof, for evening dosing
5 every 24 hours containing from about 180 mg to about 420 mg of the form of
Diltiazem with excipients to provide controlled (sustained) release of the
form of Diltiazem from the preparation for providing a C_{max} of Diltiazem in
the blood at between about 10 hours and about 17 hours (T_{max}) after
administration of the preparation, the preparation being in a sustained-
release dosage form in which the Diltiazem is adapted to be control released
10 after administration of the preparation over a period of time and being
adapted to release the Diltiazem
(i) into an aqueous medium at the following rates measured using the
method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of
water:
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(a) between about 1% and about 15% after 2 hours;
(b) between about 7% and about 35% after 4 hours;
(c) between about 30% and about 58% after 8 hours;
20 (d) between about 55% and about 80% after 14 hours; and
(e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and
about 6.5, at the following rates measured using the method of United States
25 Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 1% and about 25% after about 2 hours;

(b) between about 7% and about 45% after about 4 hours;
(c) between about 30% and about 68% after about 8 hours;
(d) in excess of about 75% after about 24 hours, wherein the preparation comprises a plurality of microgranules, wherein each 5 microgranule comprises a central core of the form of diltiazem or a pharmaceutically acceptable salt thereof, associated with a wetting agent, wherein the central core is coated with a microporous membrane in which the core and membrane comprise:

		% W/W
10	(a) Diltiazem hydrochloride	69 - 73
	(b) Microcrystalline cellulose	8 - 9.5
	(c) Povidone K30	1 - 2
	(d) Sucrose stearate	7 - 8
15	(e) Magnesium stearate NF	0.5 - 2.5
	(f) Talc USP	0.5 - 5.0
	(g) Titanium dioxide (USP)	0.15 - 0.3
	(h) Hydroxypropylmethylcellulose 2910	0.3 - 0.6
	(i) Polysorbate 80 (tween)	0.01 - 0.025
20	(j) Simeticone C emulsion USP (dry of 30%)	0.01 - 0.015
	(k) a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing).

25 64. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of

claim 63 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

65. A method of treating or preventing myocardial ischemia and angina in
5 a patient in need thereof comprising the administration of the preparation of
claim 63 to the patient in the evening for effective treatment or prevention of
the patient's myocardial ischemia and angina over a twenty-four hour
period.

10 66. A method of treating or preventing myocardial ischemia and angina in
a patient in need thereof comprising administration of a controlled-release
Galenical preparation of pharmaceutically acceptable form of Diltiazem
including the pharmaceutically acceptable salts thereof, for evening dosing
every 24 hours containing about 180 mg to about 420 mg of the form of
15 Diltiazem with excipients to provide controlled (sustained) release of the
form of Diltiazem from the preparation for providing a C_{max} of Diltiazem in
the blood at between about 10 hours and about 17 hours (T_{max}) after
administration of the preparation, the preparation being in a sustained-
release dosage form in which the Diltiazem is adapted to be control released
20 after administration of the preparation over a period of time and being
adapted to release the Diltiazem
(i) into an aqueous medium at the following rates measured using the
method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of
water:
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(a) between about 1% and about 15% after 2 hours;

- (b) between about 7% and about 35% after 4 hours;
- (c) between about 30% and about 58% after 8 hours;
- (d) between about 55% and about 80% after 14 hours; and
- (e) and in excess of about 75% after 24 hours.

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and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

- (a) between about 1% and about 25% after about 2 hours;
- (b) between about 7% and about 45% after about 4 hours;
- (c) between about 30% and about 68% after about 8 hours;
- (d) in excess of about 75% after about 24 hours, wherein the preparation comprises a plurality of microgranules, wherein each microgranule comprises a central core of the form of diltiazem or a pharmaceutically acceptable salt thereof, associated with a wetting agent, wherein the central core is coated with a microporous membrane in which the core and membrane comprise:

- (i) in the core,
 - (a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and
 - (b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with adjuvants; and

(ii) in the membrane,

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(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer; and

10 (d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with adjuvants.

15 67. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 65 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

20 68. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 65 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour period.

25 69. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising administration of a controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem

including the pharmaceutically acceptable salts thereof, for evening dosing every 24 hours containing from about 180 mg to about 420 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a C_{max} of Diltiazem in
5 the blood at between about 10 hours and about 17 hours (T_{max}) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

10 (i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;

15 (b) between about 7% and about 35% after 4 hours;

(c) between about 30% and about 58% after 8 hours;

(d) between about 55% and about 80% after 14 hours; and

(e) and in excess of about 75% after 24 hours.

20 and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 1% and about 25% after about 2 hours;

(b) between about 7% and about 45% after about 4 hours;

25 (c) between about 30% and about 68% after about 8 hours;

(d) in excess of about 75% after about 24 hours, wherein the preparation comprises a plurality of microgranules, wherein each microgranule comprises a central core of the form of diltiazem or a pharmaceutically acceptable salt thereof, associated with a wetting agent,
5 wherein the central core is coated with a microporous membrane in which the core and membrane comprise:

(i) in the core,

10 (a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

15 (b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with adjuvants; and

(ii) in the membrane,

20 (c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer;
and

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with adjuvants.

5 70. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 69 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

10 71. The method of claim 9 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with excipients and adjuvants.

15 72. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 71 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina the next morning.

20 73. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 71 to the patient in the evening for effective treatment or prevention of the patient's myocardial ischemia and angina over a twenty-four hour period.

25

74. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising administration of a controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, for evening dosing
5 every 24 hours containing from about 180 mg to about 420 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a C_{max} of Diltiazem in the blood at between about 10 hours and about 17 hours (T_{max}) after administration of the preparation, the preparation being in a sustained-
10 release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or
15 pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

20 (a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

25 (b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with adjuvants; and

(ii) in the membrane,

5 (c) between about 0.1% and about 2% of the total preparation
of water-soluble and/or water-dispersible polymer; and

10 (d) between about 5% and about 20% (% w/w of the
preparation) of a neutral copolymer of acrylic acid ethyl ester
and acrylic acid methyl ester, together with adjuvants.

75. The method of claim 74 wherein the microgranules are in capsule form.

76. The method of claim 74 wherein the microgranules are in tablet form.

15 77. The method of claim 74 wherein the core and membrane
comprise:

(i) in the core,

20 (a) between about 69% and about 73% (% w/w of the total
preparation) of Diltiazem or pharmaceutically acceptable salt
thereof; and

25 (b) between about 7% and about 8% wetting agent (% w/w of
the total preparation);

together with adjuvants; and

(ii) in the membrane,

5

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer; and

10

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with adjuvants.

78. A method of treating or preventing myocardial ischemia and angina in
15 a patient in need thereof comprising administration of a controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, for evening dosing every 24 hours containing from about 180 mg to about 420 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the
20 form of Diltiazem from the preparation for providing a C_{max} of Diltiazem in the blood at between about 10 hours and about 17 hours (T_{max}) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the
25 preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a

microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

5 (i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

10 (b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with adjuvants; and

15 (ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer; and

20 (d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with adjuvants wherein the core and membrane comprise:

25	%	W/W
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(a) Diltiazem hydrochloride	69 - 73
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(b)	Microcrystalline cellulose (Avicel ph101)	8 - 9.5
(c)	Povidone K30	1 - 2
(d)	Sucrose stearate (crodesta F150)	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
5 (f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween)	0.01 - 0.025
(j)	Simeticone C emulsion USP (dry of 30%)	0.01 - 0.015
10 (k)	a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing).

15 79. The method of claim 74 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with excipients and adjuvants.

20

80. A method of treating or preventing myocardial ischemia and angina in a patient in need thereof comprising the administration of the preparation of claim 74 to the patient in the evening for effective treatment of the myocardial ischemia the next morning.

25

81. The method of claim 1 in capsule form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises a form 5 of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.

82. The method of claim 1 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total 10 amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.

15

83. The method of claim 1 in tablet form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises a form of Diltiazem 20 or pharmaceutically acceptable salt thereof associated with a wetting agent.

84. The method of claim 1 in tablet form wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises a form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.

10 85. The method of claim 1 in capsule form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises a form of Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the 15 wetting agent.

86. The method of claim 1 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total 20 amount of active per hour during dissolution, and wherein the preparation is

a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and
5 wherein the Diltiazem is mixed (in whole or in part) with the wetting agent.

87. The method of claim 1 in tablet form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a
10 microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent wherein the Diltiazem is mixed (in whole or in part) with the wetting agent.

88. The method of claim 1 in tablet form wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of
15 active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt

thereof associated with a wetting agent and wherein the Diltiazem is mixed
(in whole or in part) with the wetting agent.

89. The method of claim 1 in capsule form wherein the
5 preparation is a diffusion controlled preparation and wherein each
microgranule comprising a central core containing the form of diltiazem
coated with a microporous membrane and the central core comprises
Diltiazem or pharmaceutically acceptable salt thereof associated with a
wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the
10 wetting agent wherein the wetting agent assists to maintain the solubility of
the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is
unaffected by the pH of the gastrointestinal tract or other adverse conditions
which the composition will meet therein.

15 90. The method of claim 1 in capsule form, wherein the
preparation releases the Diltiazem at a rate of less than about 15% of the total
amount of active per hour during dissolution, and wherein the preparation is
a diffusion controlled preparation and wherein each microgranule
comprising a central core containing the form of diltiazem coated with a
20 microporous membrane and the central core comprises Diltiazem or

pharmaceutically acceptable salt thereof associated with a wetting agent and
wherein the Diltiazem is mixed (in whole or in part) with the wetting agent
wherein the wetting agent assists to maintain the solubility of the Diltiazem
in each bead, ensuring that the solubility of the Diltiazem is unaffected by the
5 pH of the gastrointestinal tract or other adverse conditions which the
composition will meet therein.

91. The method of claim 1 in tablet form wherein the preparation
is a diffusion controlled preparation and wherein each microgranule
10 comprising a central core containing the form of diltiazem coated with a
microporous membrane and the central core comprises Diltiazem or
pharmaceutically acceptable salt thereof associated with a wetting agent
wherein the Diltiazem is mixed (in whole or in part) with the wetting agent
wherein the wetting agent assists to maintain the solubility of the Diltiazem
15 in each bead, ensuring that the solubility of the Diltiazem is unaffected by the
pH of the gastrointestinal tract or other adverse conditions which the
composition will meet therein.

92. The method of claim 1 in tablet form wherein the preparation
20 releases the Diltiazem at a rate of less than about 15% of the total amount of

active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt

5 thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

10

93. The method of claim 1 in capsule form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein wherein the membrane comprises a

water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

5

94. The method of claim 1 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule

10 comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem

15 in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic

20 acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

95. The method of claim 1 in tablet form wherein the preparation
is a diffusion controlled preparation and wherein each microgranule
comprising a central core containing the form of diltiazem coated with a
5 microporous membrane and the central core comprises Diltiazem or
pharmaceutically acceptable salt thereof associated with a wetting agent
wherein the Diltiazem is mixed (in whole or in part) with the wetting agent
wherein the wetting agent assists to maintain the solubility of the Diltiazem
in each bead, ensuring that the solubility of the Diltiazem is unaffected by the
10 pH of the gastrointestinal tract or other adverse conditions which the
composition will meet therein and wherein the membrane comprises a water-
dispersible or water-soluble polymer and a water-, acid- and base-insoluble
polymer of a neutral acrylic polymer including a neutral copolymer of acrylic
acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

15

96. The method of claim 1 in tablet form wherein the preparation
releases the Diltiazem at a rate of less than about 15% of the total amount of
active per hour during dissolution, and wherein the preparation is a diffusion
controlled preparation and wherein each microgranule comprising a central
20 core containing the form of diltiazem coated with a microporous membrane

and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the
5 solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic
10 acid methyl ester which hydrates the preparation.

97. The method of claim 1 in capsule form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem
15 coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is
20 unaffected by the pH of the gastrointestinal tract or other adverse conditions

which the composition will meet therein wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the
5 preparation wherein the membrane further comprises hydroxypropylmethylcellulose.

98. The method of claim 1 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total
10 amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and
15 wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-
20 dispersible or water-soluble polymer and a water-, acid- and base-insoluble

polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose.

5 99. The method of claim 1 in tablet form wherein the preparation
is a diffusion controlled preparation and wherein each microgranule
comprising a central core containing the form of diltiazem coated with a
microporous membrane and the central core comprises Diltiazem or
pharmaceutically acceptable salt thereof associated with a wetting agent
10 wherein the Diltiazem is mixed (in whole or in part) with the wetting agent
wherein the wetting agent assists to maintain the solubility of the Diltiazem
in each bead, ensuring that the solubility of the Diltiazem is unaffected by the
pH of the gastrointestinal tract or other adverse conditions which the
composition will meet therein and wherein the membrane comprises a water-
15 dispersible or water-soluble polymer and a water-, acid- and base-insoluble
polymer of a neutral acrylic polymer including a neutral copolymer of acrylic
acid ethyl ester and acrylic acid methyl ester which hydrates the preparation
wherein the membrane further comprises hydroxypropylmethylcellulose.

100. The method of claim 1 in tablet form wherein the preparation
a diffusion controlled preparation and wherein each microgranule
comprising a central core containing the form of diltiazem coated with a
microporous membrane and the central core comprises Diltiazem or
5 pharmaceutically acceptable salt thereof associated with a wetting agent
wherein the Diltiazem is mixed (in whole or in part) with the wetting agent
wherein the wetting agent assists to maintain the solubility of the Diltiazem
in each bead, ensuring that the solubility of the Diltiazem is unaffected by the
pH of the gastrointestinal tract or other adverse conditions which the
10 composition will meet therein and wherein the membrane comprises a water-
dispersible or water-soluble polymer and a water-, acid- and base-insoluble
polymer of a neutral acrylic polymer including a neutral copolymer of acrylic
acid ethyl ester and acrylic acid methyl ester which hydrates the preparation
wherein the membrane further comprises hydroxypropylmethylcellulose.

15

101. The method of claim 1 in capsule form wherein the
preparation is a diffusion controlled preparation and wherein each
microgranule comprising a central core containing the form of diltiazem
coated with a microporous membrane and the central core comprises
20 Diltiazem or pharmaceutically acceptable salt thereof associated with a

wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions

- 5 which the composition will meet therein wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises
- 10 hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).
- 15

102. The method of claim 1 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is
- 20 a diffusion controlled preparation and wherein each microgranule

comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent

- 5 wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble
- 10 polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid
- 15 penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).

103. The method of claim 1 in tablet form wherein the preparation
- 20 is a diffusion controlled preparation and wherein each microgranule

comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent wherein the Diltiazem is mixed (in whole or in part) with the wetting agent

5 wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble

10 polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid

15 penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).

104. The method of claim 1 in tablet form wherein the preparation
20 releases the Diltiazem at a rate of less than about 15% of the total amount of

active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt
5 thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and
10 wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane
15 hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).

105. The method of claim 1 in capsule form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises

5 Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions

10 which the composition will meet therein wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises

15 hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 180 mg of Diltiazem.

20

106. The method of claim 1 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is
5 a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent
10 wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble
15 polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid
20 penetrates and hydrates the bead, and dissolves the diltiazem and wetting

agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 180 mg of Diltiazem.

5 107. The method of claim 1 in tablet form wherein the preparation
is a diffusion controlled preparation and wherein each microgranule
comprising a central core containing the form of diltiazem coated with a
microporous membrane and the central core comprises Diltiazem or
pharmaceutically acceptable salt thereof associated with a wetting agent
10 wherein the Diltiazem is mixed (in whole or in part) with the wetting agent
wherein the wetting agent assists to maintain the solubility of the Diltiazem
in each bead, ensuring that the solubility of the Diltiazem is unaffected by the
pH of the gastrointestinal tract or other adverse conditions which the
composition will meet therein and wherein the membrane comprises a water-
15 dispersible or water-soluble polymer and a water-, acid- and base-insoluble
polymer of a neutral acrylic polymer including a neutral copolymer of acrylic
acid ethyl ester and acrylic acid methyl ester which hydrates the preparation
wherein the membrane further comprises hydroxypropylmethylcellulose and
wherein the membrane hydrates the core within the membrane which when
20 put in gastrointestinal fluid causes the membrane to swell while fluid

penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 180 mg of Diltiazem.

5

108. The method of claim 1 in tablet form wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the 15 solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane 20

further comprises hydroxypropylmethylcellulose and wherein the membrane
hydrates the core within the membrane which when put in gastrointestinal
fluid causes the membrane to swell while fluid penetrates and hydrates the
bead, and dissolves the diltiazem and wetting agent and benefits from a
5 concentration gradient through the membrane (high concentration inside and
low concentration outside) wherein the preparation contains 180 mg of
Diltiazem.

109. The method of claim 1 in capsule form wherein the
10 preparation is a diffusion controlled preparation and wherein each
microgranule comprising a central core containing the form of diltiazem
coated with a microporous membrane and the central core comprises
Diltiazem or pharmaceutically acceptable salt thereof associated with a
wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the
15 wetting agent wherein the wetting agent assists to maintain the solubility of
the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is
unaffected by the pH of the gastrointestinal tract or other adverse conditions
which the composition will meet therein wherein the membrane comprises a
water-dispersible or water-soluble polymer and a water-, acid- and base-
20 insoluble polymer of a neutral acrylic polymer including a neutral copolymer

of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the
5 membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 360 mg of Diltiazem.

10 110. The method of claim 1 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a
15 microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the
20 pH of the gastrointestinal tract or other adverse conditions which the

composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation

- 5 wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane
- 10 (high concentration inside and low concentration outside) wherein the preparation contains 360 mg of Diltiazem.

111. The method of claim 1 in tablet form wherein the preparation is a diffusion controlled preparation and wherein each microgranule
15 comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem
20 in each bead, ensuring that the solubility of the Diltiazem is unaffected by the

pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the Diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 360 mg of Diltiazem.

112. The method of claim 1 in tablet form wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of Diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed

(in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and

5 wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane

10 hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 360 mg of

15 Diltiazem.

113. The method of claim 1 in capsule form wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem

20 coated with a microporous membrane and the central core comprises

Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is
5 unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the
10 preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration
15 gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 420 mg of Diltiazem.

114. The method of claim 1 in capsule form, wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total
20 amount of active per hour during dissolution, and wherein the preparation is

a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and

5 wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble

10 polymer of a neutral acrylic polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane hydrates the core within the membrane which when

15 put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 420 mg of Diltiazem.

115. The method of claim 1 in tablet form wherein the preparation
is a diffusion controlled preparation and wherein each microgranule
comprising a central core containing the form of diltiazem coated with a
microporous membrane and the central core comprises Diltiazem or
5 pharmaceutically acceptable salt thereof associated with a wetting agent
wherein the Diltiazem is mixed (in whole or in part) with the wetting agent
wherein the wetting agent assists to maintain the solubility of the Diltiazem
in each bead, ensuring that the solubility of the Diltiazem is unaffected by the
pH of the gastrointestinal tract or other adverse conditions which the
10 composition will meet therein and wherein the membrane comprises a water-
dispersible or water-soluble polymer and a water-, acid- and base-insoluble
polymer of a neutral acrylic polymer including a neutral copolymer of acrylic
acid ethyl ester and acrylic acid methyl ester which hydrates the preparation
wherein the membrane further comprises hydroxypropylmethylcellulose and
15 wherein the membrane hydrates the core within the membrane which when
put in gastrointestinal fluid causes the membrane to swell while fluid
penetrates and hydrates the bead, and dissolves the diltiazem and wetting
agent and benefits from a concentration gradient through the membrane
(high concentration inside and low concentration outside) wherein the
20 preparation contains 420 mg of Diltiazem.

116. The method of claim 1 in tablet form wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution, and wherein the preparation is a diffusion controlled preparation and wherein each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent and wherein the Diltiazem is mixed (in whole or in part) with the wetting agent wherein the wetting agent assists 5 to maintain the solubility of the Diltiazem in each bead, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein and wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic 10 polymer including a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation wherein the membrane further comprises hydroxypropylmethylcellulose and wherein the membrane 15 hydrates the core within the membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the bead, and dissolves the diltiazem and wetting agent and benefits from a 20

concentration gradient through the membrane (high concentration inside and low concentration outside) wherein the preparation contains 420 mg of Diltiazem.